Phthalides

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T1: Phytotherapy Research, Vol. 11, 576—582 (1997)

Cardiovascular Pharmacology of 3-n-butylphthalide in Spontaneously Hypertensive Rats

D. Tsi and B. K. H. Tan

The hypotensive and vasorelaxant effects of 3-n-butylphthalide (BuPh) and its possible m
were investigated in spontaneously hypertensive rats (SHR) for the first time. A 13-day int
of BuPh at doses of 2.0 and 4.0 mg/day produced a transient hypotensive effect while a d
showed a significant hypotensive effect only on day 12. BuPh at 0.5 mg/day had no effect
tissue angiotensin converting enzyme (ACE) activities, or on the tissue lipid peroxidation l
endothelium-intact and denuded aortic rings precontracted with phenylephrine and KCl. N
methyl ester, an inhibitor of nitric oxide synthase, did not attenuate the vasorelaxant activi
cumulative concentration response curves of phenylephrine and Ca 2+ (in CaCl2 -free, hig
were non-competitively inhibited by BuPh. However, BuPh did not interfere with the caffei
of intracellular Ca 2+ . it appears that the vasorelaxant effect of BuPh could be attributed t
Ca 2+ entry, possibly through voltage- and receptor-operated Ca 2+ channels, thereby low
blood pressure of SHR.

2: Acta Pharmacol Sin 2000 May;21(5):433-8

Inhibitory effects of chiral 3-n-butylphthalide on inflammation following focal ischemic brain

Xu HL, Feng YP.

AIM: To evaluate the degree of neutrophil infiltration into ischemic tissue after transient foc
ischemia, and to examine the effects of chiral 3-n-butylphthalide (NBP) on this inflammato
METHODS: After a 24-h reperfusion following transient cerebral ischemia, two different te
analysis and modified myeloperoxidase (MPO)-quantification method, were utilized to ider

neutrophils into cerebral tissue following ischemia. The expression of intercellular adhesio (ICAM-1) and tumor necrosis factor-alpha(TNF-alpha) in the ischemic zone were observec immunohistochemistry, Western blot, and in situ hybridization techniques.

RESULTS: In cerebral cortex area perfused by middle cerebral artery (MCA), MPO activity increased after 24 h of reperfusion in the vehicle group, and it correlated well with the infilt neutrophils. Administration of dl-, d-, and l-NBP (20 mg.kg-1) partially inhibited both the inc activity and the appearance of neutrophils in ischemia-reperfusion sites. Up-regulation of I observed on the microvessel endothelium in the ischemic territory. In addition, chiral NBP ICAM-1 expression, and decreased the number of TNF-alpha blue purple-positive neurons ischemia-reperfusion injury. CONCLUSION: The results indicate that the increase in neutr into the infarct site implicated postischemic brain injury, and NBP was effective in protectir sites following ischemic insult.

PMID: 11324442 [PubMed - indexed for MEDLINE]

3: Yakugaku Zasshi 1989 Jun;109(6):402-6

[Centrally acting muscle relaxant effect of phthalides (ligustilide, cnidilideand senkyunolide Cnidium officinale Makino] [Article in Japanese]Ozaki Y, Sekita S, Harada M.
The present study was carried out to elucidate a centrally acting musclerelaxant effect of c fraction and its component, namely, ligustilide, cnidilide and senkyunolide obtained from th Cnidium officinale Makino. These three compounds were isolated from the chloroform solu column chromatography on silica gel. The centrally acting muscle relaxant effect was inve crossed extensor reflex in anesthetized rats and these samples were suspended in 0.5% c cellulose solution and administered i.p. These three compounds as well as the chloroform depressed the reflex response. The depressive potencies among them were almost the sa potencies were also the same or somewhat weaker as that of mephenesin. As a curare-lik observed, a muscle relaxation induced by these phthalide compounds is considered to be origin.PMID: 2810059 [PubMed - indexed for MEDLINE]

4: Clin Exp Pharmacol Physiol 1999 Oct;26(10):845-6

NBPA: a cerebral ischemic protective agent.

Zhang J, Peng X, Wei G, Su D.

1. NBPA is a derivative of 3-n-butylphathalide isolated from Apium graveolens Linn.

2. At concentrations ranging from 6 x 10(-6) to 10(-6) mol/L, NBPA inhibited the L-type cal guinea-pig myocardial cells and cultured human neuroblastoma cells.

3. At 10(-6) mol/L, NBPA markedly inhibited calcium-dependent and -independent release

synaptosomes.

4. The [31P] nuclear magnetic resonance spectrum has shown that pretreatment with NBI improved energy metabolism.

5. In situ hybridization has shown that 10 and 20 mg/kg, i.p., NBPA prior to cerebral artery accelerate the expression of heat shock protein 70 mRNA and inhibit c-fos mRNA expres

6. It has been shown that NBPA decreases the nitric oxide content and bc nitric oxide synt in the global cerebral ischaemia-reperfusion model in rats. In addition, it has been shown t significantly inhibits the expression of inducible NOS protein.

PMID: 10549420 [PubMed - indexed for MEDLINE]

5: Bioorg Med Chem 1999 Jul;7(7):1445-50

Structure-requirements of isocoumarins, phthalides, and stilbenes from

Hydrangeae Dulcis Folium for inhibitory activity on histamine release from rat

peritoneal mast cells.

Matsuda H, Shimoda H, Yoshikawa M.

We examined the structure-activity relationships of isocoumarins, phthalides and stilbenes Hydrangeae Dulcis Folium and related compounds for the inhibition of histamine release fr mast cells. The activities of isocoumarins such as thunberginols A and B were more potent dihydroisocoumarins such as hydrangenol and thunberginol G. The double bond at the 3-p be essential to potentiate the activity. The hydroxyl groups at the 8-, 3'- and 4'-positions of essential for the activity, while the hydroxyl group at the 6-position was scarcely needed. S of benzylidenephthalides such as thunberginol F were more potent than those of hydrama the presence of a double bond at the 3-position was needed to increase the activity. More group at the 8-position was essential for the activity. On the time course study, thunbergin completely inhibited histamine release by pretreatment at 100 microM for 1 to 15 min, whe inhibited histamine release only following 1-min pretreatment at 1000 microM. These resul the mechanisms of the inhibitory effect of thunberginols are different from that of DSCG.

PMID: 10465418 [PubMed - indexed for MEDLINE]

6: Life Sci 1998;62(23):2073-82

Effects of methylenechloride-solubie fraction of Japanese angelica root extract, ligustilide butylidenephthalide, on pentobarbital sleep in group-housed and socially isolated mice.

Matsumoto K, Kohno S, Ojima K, Tezuka Y, Kadota S, Watanabe H.

We previously showed that the extract of Japanese angelica root (JAR-E) reversed the de pentobarbital (PB) sleep induced by isolation stress and yohimbine and methoxamine, stir noradrenergic systems, in mice. Here, we tested the effects of several fractions from JAR butylidenephthalide, phthalide components of JAR-E, on PB sleep in isolated mice to eluc mechanism of the action of JAR-E. Methanol-soluble (Met-S) and -insoluble (Met-IS) fracti from JAR-E. Methylenechloride-soluble (MC-S) and -insoluble fractions (MC-IS) were prep MC-S (11.4-76 mg/kg, p.o.) reversed the isolation stress-induced decrease in PB sleep, bu (0.8-2.4 g/kg, p.o.) nor MC-IS (0.7-2 g/kg, p.o.) had the same effect. The i.p. administratio a similar activity to that observed after the p.o. administration of the same fraction. Ligustil i.p.) and butylidenephthalide (10-30 mg/kg, i.p.) reversed PB sleep decrease in isolated m components (20 mg/kg, i.p.) attenuated the suppressive effects of yohimbine (30 nmol, i.c (200 nmol, i.c.v.) and a benzodiazepine inverse agonist FG7142 (10 mg/kg, i.p.) on PB sle mice. These results suggest the contribution of ligustilide and butylidenephthalide to the el PB sleep in isolated mice, and implicate central noradrenergic and/or GABA(A) systems ir components.

PMID: 9627086 [PubMed - indexed for MEDLINE]

7: Jpn J Pharmacol 1980 Feb;30(1):85-91

A newly isolated antispasmodic--butylidenephthalide.

Ko WC.

Butylidenephthalide (BdPh), ligustilide and butylphthalide were isolated and purified from r Ligusticum wallichii Franch. Among these three, BdPh proved to be the most active in inhi contractions induced by prostaglandin F2 alpha, oxytocin and ACh. In studies done to com BdPh and papaverine (Pap), guinea pig ileum, vas deferens and taenia coli were used. Bo contractile responses of the ileum to agonists including ACh, K+ and Ba2+ in normal Tyro exogenous Ca2+ in high K+ (80 mM), Ca2+-free Tyrode solution, and also responses of v responses to norepinephrine. Thus, BdPh is a non-specific antispasmodic but weaker in p However, as the inhibitory effects of BdPh on phasic contraction (PC) and tonic contractio preparations, including depolarized and non-depolarized ileum and taenia coli, were much suggested that the action mechanism of BdPh may differ from that of Pap which inhibited than PC. It may be concluded that BdPh possesses an non-specific antispasmodic action

Pap, the mechanism of action being different from that of Pap.

PMID: 7401411 [PubMed - indexed for MEDLINE]

8. Zhongguo Yao Li Xue Bao. 1999 Oct;20(10):929-33.

Effects of 3-n-butylphthalide on production of vasoactive substances by cerebral and aorti
Xu HL, Feng YP. Institute of Materia Medica, Chinese Academy of Medical Sciences, Pek
College, Beijing 100050, China. AIM:

The effects of dl-3-n-butylphthalide (dl-NBP), l-3-n-butylphthalide (l-NBP), and d-3-n-butyl
on the production of nitric oxide (NO), epoprostenol (Epo) and endothelin-1 (ET-1) were in
cerebrovascular and aortic endothelium in culture. METHODS: Bovine cerebral endothelia
bovine aortic endothelial cells (BAEC) were cultured in Medium 199 in vitro. After incubatir
NBP for 24 h, the release of NO, Epo, and ET-1 were analyzed by using spectrometry ass
radioimmunoassay (RIA) respectively. RESULTS: Low concentrations of dl- and l-NBP (0.
enhanced nitrite and 6-ketoprostaglandin F1 alpha (6-ketoPGF1 alpha) production in both
after a 24-h incubation, and l-NBP has a potent effect on promoting Epo production in BCE
of ET-1 secreted by BCEC and BAEC was increased after TNF alpha stimulation, this enh
blunted by the simultaneous addition of dl-, l-, and d-NBP. CONCLUSION: 1) dl-NBP and
production in both BCEC and BAEC. 2) l-NBP increases more Epo production in BCEC th
and dl-NBP has selective effect on increasing Epo production in BCEC.

PMID: 11270994 [PubMed - indexed for MEDLINE]

**9. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from Api
Linn. seeds.**

Momin RA, Nair MG. Department of Horticulture and National Food Safety and Toxicology
State University, East Lansing 48824, USA. Phytomedicine. 2002 May;9(4):312-8.

Cyclooxygenase inhibitory and antioxidant bioassay-directed extraction and purification of
yielded sedanolide (1), senkyunolide-N (2), senkyunolide-J (3), 3-hydroxymethyl-6-metho
indol-2-ol (4), L-tryptophan (5), and 7-[3-(3,4-dihydroxy-4-hydroxymethyl-tetrahydro-furan-
dihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-yloxy]-5-hydroxy-2-(4-hydroxy-3-methoxy-p
one (7). The structures of compounds 1-7 were determined using spectroscopic methods.
reported here for the first time. At 250 pg ml(-1), compounds 1-4, 6 and 7 displayed proste
endoperoxide synthase-I (COX-I) and prostaglandin H endoperoxide synthase-II (COX-II)
at pH 7. The acetylated product (5) of compound 4 also inhibited COX-I and COX-II enzym
250 microg ml(-1). Compounds 6 and 7 exhibited good antioxidant activity at concentratio
microg ml(-1). Only compounds 1-3 exhibited topoisomerase-I and -II enzyme inhibitory ac
concentrations of 100, 200 and 200 microg ml(-1), respectively.

PMID: 12120812 [PubMed - indexed for MEDLINE]

10. NSAID gastropathy: prevention by celery seed extracts in disease-stressed rats

Whitehouse M.W., Butters. DE, Clarke M L, Rainsford K D

Inflammopharmacology, Vol 9, No 1.2, pp 201 -209 (2001)